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Diarrhea with epidermal growth factor receptor tyrosine kinase inhibitors in cancer patients: A meta-analysis of randomized controlled trials

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ABSTRACT

We performed an meta-analysis to fully investigate the diarrhea of EGFR-TKIs in cancer patients. The relevant studies of the randomized controlled trials (RCTs) in cancer patients treated with EGFR-TKIs were retrieved and the systematic evaluation was conducted. EMBASE, MEDLINE, and PubMed were searched for articles published till August 2017. The relevant RCTs in cancer patients treated with EGFR-TKIs were retrieved and the systematic evaluation was conducted. Twenty-four RCTs and 13,748 patients were included. The current analysis suggested that the use of EGFR-TKIs increased the risk of all-grade diarrhea (RR 3.45; 95%CI, 2.94–4.06; $p < 0.00001$) and high-grade ($\geq$ grade 3) diarrhea (RR 8.22 ; 95%CI, 6.02–11.23; $p < 0.00001$). On subgroup analysis, the risk of all-grade and high-grade diarrhea varied significantly within drug type. The risk of all-grade diarrhea varied significantly according to cancer type, whereas the risk of high-grade diarrhea did not. The risk of all-grade and high-grade diarrhea did not varied significantly based on treatment line, treatment duration and median age. The available data suggested that the use of EGFR-TKIs is associated with a significantly increased risk of diarrhea in cancer patients.

1. Introduction

The epidermal growth factor receptor signaling pathway plays a crucial role in regulating tumorigenesis and cell survival and may be important in the development and progression of cancer (Lee et al., 2013). It represents an important target in cancer drug development (Cohen et al., 2010). Indeed, two small molecular agents that target the tyrosine kinase domain of the EGFR, erlotinib and gefitinib, are approved in many countries for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) as second- or third-line therapy (Cohen et al., 2004; Jänne et al., 2005; Sequist et al., 2015). And second generation tyrosine kinase inhibitors, such as afatinib and neratinib, have undergone evaluation among different epithelial cancers (Awada et al., 2013; Tsai et al., 2013). In addition, the efficacy and safety of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) such as vandetanib, dacomitinib and lapatinib has also been investigated (Arnold et al., 2007; Ellis et al., 2014; Del Campo et al., 2011).

EGFR-TKIs lack the typical adverse effects of traditional chemotherapy agents, but several drug-related dermatologic toxicities such as acneiform rash, fatigue and diarrhea have been frequently reported (Citri and Yarden, 2006). Diarrhea is one of the most common toxicities caused by systemic chemotherapy (Rubenstein et al., 2004), although these toxicities in many cases are clinically manageable, however they can significantly affect patient quality of life and increase treatment costs. Moreover, severe diarrhea can result in fluid and electrolyte losses, leading to dehydration, electrolyte imbalances and renal insufficiency, in addition to nutritional deficiencies (Hirsh, 2011). Therefore, it is necessary to shed more light on this common side effect. However, the risk of diarrhea in cancer patients treated with EGFR-TKIs varies widely across clinical trials, and risk factors underlying the variation are still unclear. Therefore, we conducted this meta-analysis of 24 randomized controlled trials (RCTs) to fully investigate the diarrhea of EGFR-TKIs in patients with cancer.

2. Patients and methods

2.1. Search strategy and study selection

Study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) (Supplementary Table 2). An independent review (by two reviewers: *J* L and *J* G) of citations from PubMed/Medline from January 1, 1966 to August 31, 2017 was conducted. Databases were searched using combinations of the following keywords 'gefitinib', 'erlotinib', 'afatinib', 'vandetanib', 'dacomitinib', 'icotinib', 'lapatinib',

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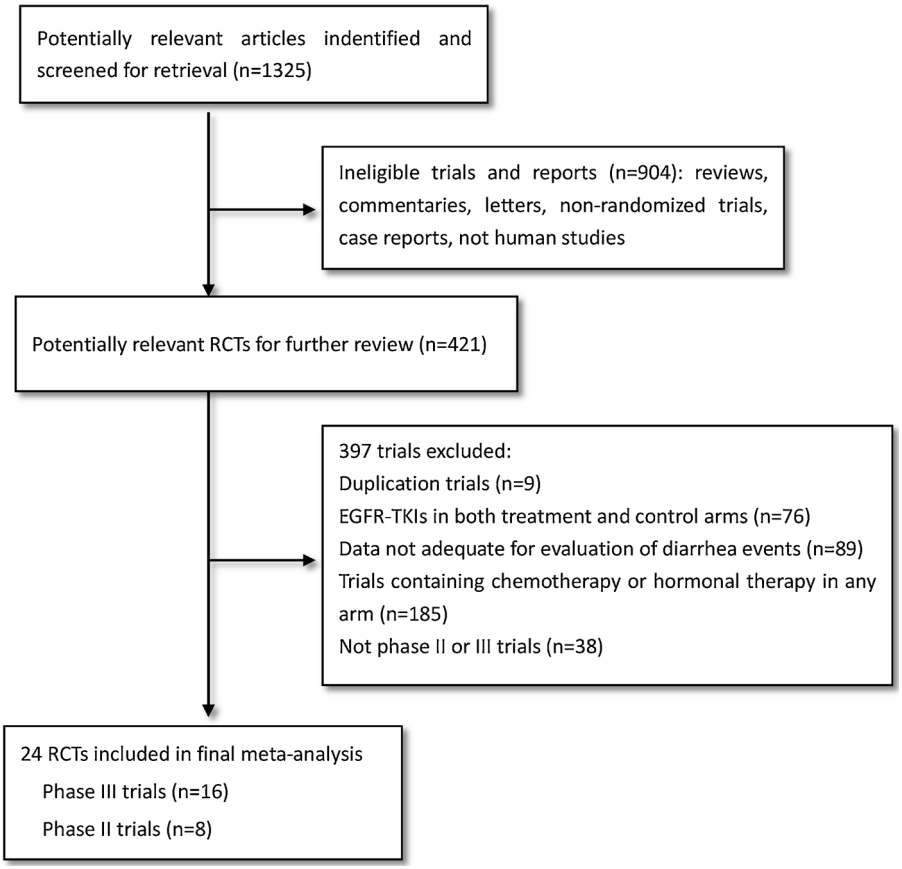

Fig. 1. Flow chart showing the selection of studies included in the present review (RCTs, randomized controlled trials).

'osimertinib', 'neratinib', 'tumor' and 'cancer'. The search was limited to RCTs published in English. We also performed independent searches using EMBASE between January 1, 1974, and August 31, 2017, to ensure that no clinical trials were overlooked. Additionally, we searched the clinical trial registration website to obtain information on the registered trials between January 2004 and August 2017. At each screening level, investigators of the review team selected articles for inclusion independently after an initial calibration exercise. RCTs met the following criteria were included: (1) Randomized controlled phase II and III trials in patients with cancer. (2) Participants assigned to treatment with one of these agents daily. (3) Events or event rate and sample size available for diarrhea/diarrhoea. (4) Only trials containing pure placebo, best supportive care, observation or no therapy in the control arm were included.

As chemotherapeutic agents, hormonal agents or corticosteroids may modulate diarrhea, we excluded trials where these agents were used concurrently.

2.2. Data extraction

We extracted details on first author's name, year of publication, trial phase, number of enrolled subjects, treatment arms, number of patients in treatment and controlled groups, underlying malignancy, median age, median treatment duration, adverse outcomes of interest (all-grade and high-grade diarrhea), name and dosage of the EGFR-TKIs agents and other anti-cancer agents. For this study, we separated diarrhea into all grades (grade 1–5) and high-grade (grade 3–5) for our analysis. Data were extracted by one investigator and checked by another investigator. If a particular patient population was reported in more than one publication with the same outcome parameters, the article providing the most detailed data was included in the meta-analysis. The co-primary end points of the study were high-grade and all-grade diarrhea. Diarrhea was defined as per versions 2.0, 3.0 or 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) criteria.

2.3. Quality assessment

Each study was independently assessed for quality and for potential bias by two reviewers based on randomization procedure; allocation concealment; blinding; study withdrawals; intention-to-treat (ITT) analyses; and comparability between groups at baseline. Two reviewers (J L, J G) independently assessed each study for quality and risk of bias using the Jadad ranking system (Jadad et al., 1996). Disagreements were resolved by consensus.

2.4. Data analysis

Data were calculated by Review Manager Version 5.2. For the outcomes, the risk ratio (RR) was calculated for dichotomous data. A 95% confidence interval (CI) was calculated for all types of data. Heterogeneity was quantified by calculating the I^2 statistic. An I^2 estimate greater than 50% was regarded as indicating a high level of heterogeneity and its causes were investigated. Subgroup analysis was conducted to examine whether the RRs of all-grade and high-grade diarrhea varied by the type of drug, line of therapy (first line, ≥second line or maintenance), type of cancer (NSCLC vs. non-NSCLC), duration of therapy (< 6 months vs. ≥ 6 months), and age (≤60 years vs. > 60 years).

3. Results

The literature search yielded 1325 potentially relevant trials. The initial screening excluded 904 trials for at least one of the following

reasons: reviews, commentaries, letters, non-randomized trials, case reports, not human studies or not in English. The remaining 421 RCTs were carefully screened, and an additional 397 were excluded for not phase II or III trials or other reasons. The remaining 24 trials were judged as eligible for the present meta-analysis (16 phase II and 8 phase III trials, Fig. 1) (Arnold et al., 2007; Lee et al., 2012a; Ahn et al., 2013; Hsu et al., 2012; Wells et al., 2012; Leboulleux et al., 2012; Thatcher et al., 2005; Zhang et al., 2012; Goss et al., 2009; Dutton et al., 2014; Gaafar et al., 2011; Goss et al., 2013a; Cappuzzo et al., 2010; Kelly et al., 2015; Lee et al., 2012b; Shepherd and Rodrigues Pereira, 2005; Miller et al., 2012; Ellis et al., 2014; Harrington et al., 2015; Powles et al., 2017; Decensi et al., 2011; Del Campo et al., 2011; Harrington et al., 2013; Goss et al., 2013b).

3.1. Characteristics of included studies

A total of 13748 patients were available for the meta-analysis. When examining by agent, vandetanib was investigated in 6 trials (Arnold et al., 2007; Lee et al., 2012a; Ahn et al., 2013; Hsu et al., 2012; Wells et al., 2012; Leboulleux et al., 2012), gefitinib in 6 trials (Thatcher et al., 2005; Zhang et al., 2012; Goss et al., 2009; Dutton et al., 2014; Gaafar et al., 2011; Goss et al., 2013a), erlotinib in 4 trials (Cappuzzo et al., 2010; Kelly et al., 2015; Lee et al., 2012b; Shepherd and Rodrigues Pereira, 2005), afatinib in 1 trial (Miller et al., 2012), dacomitinib in 1 trial (Ellis et al., 2014), lapatinib in 6 trials (Harrington et al., 2015; Powles et al., 2017; Decensi et al., 2011; Del Campo et al., 2011; Harrington et al., 2013; Goss et al., 2013b). The most common underlying malignancies represented were small-cell lung cancer (SCLC) (Arnold et al., 2007), NSCLC (Lee et al., 2012a; Ahn et al., 2013; Thatcher et al., 2005; Zhang et al., 2012; Goss et al., 2009; Gaafar et al., 2011; Ellis et al., 2014), hepatocellular carcinoma (HCC) (Hsu et al., 2012), thyroid cancer (Wells et al., 2012; Leboulleux et al., 2012), oesophageal cancer (Dutton et al., 2014), squamous cell carcinoma (SCC) (Harrington et al., 2015; Del Campo et al., 2011; Harrington et al., 2013), bladder cancer (Powles et al., 2017), and breast cancer (Decensi et al., 2011; Goss et al., 2013b). The methods of randomization were reported in 19 studies. Twenty-two of these studies were double-blinded studies, one was single-blinded study, and 1 was open-label study. Concealment was reported in 9 studies. Intention-to-treat (ITT) analysis was conducted in 21 studies. Follow-up time was generally adequate for each trial and included a period of approximately 2–6 weeks after end of therapy on trial. All of these RCTs were judged to be of adequate quality (jadad score $\geq$3/5). The characteristics of the included trials are summarized in Table 1, and the quality assessment of the included trials are summarized in Supplementary Table 1.

3.2. Risk ratio (RR) of all-grade diarrhea

All-grade diarrhea occurred in 3605 of 7239 (49.8%) patients in the EGFR-TKIs arms, and 698 of 5222 (13.4%) in the placebo arms. A meta-analysis of the RR of all-grade diarrhea was performed on the 22 RCTs (Fig. 2). The RR of all-grade diarrhea was 3.45 (95%CI, 2.94-4.06 ; $p < 0.00001$). Thus, patients treated with these agents had a significant increased risk of all-grade diarrhea. Significant heterogeneity was detected among the studies ($p < 0.00001$, $I^2 = 71\%$), which might be due to the different drug types, tumor types or line of therapy. Therefore, subgroup analyses were preformed according to these differences.

3.3. Risk ratio (RR) of high-grade diarrhea

High-grade($\geq$grade 3)diarrhea occurred in 500 of 7759 (6.4%) patients in the EGFR-TKIs arms, and 42 of 5751 (0.7%) in the placebo arms. A meta-analysis of the RR of high-grade diarrhea was performed on the 21 RCTs (Fig. 3). The RR of high-grade diarrhea was 8.22 (95%CI, 6.02–11.23 ; $p < 0.00001$). Thus, patients treated with these agents had a significant increased risk of high-grade diarrhea. There was no statistically significant heterogeneity($I^2 = 26\%$)across the trials.

3.4. Subgroup analysis

3.4.1. Subgroup analysis according to the agent used

In order to explore the impact of individual agents on the RRs of diarrhea, we calculated RRs according to the type of agent used. For both all-grade ($p < 0.0001$, Table 2) and high-grade ($p = 0.02$, Table 3) diarrhea, there were significant differences in the RRs by type of drug. Afatinib was associated with the highest risk of all-grade (RR = 9.42) and high-grade (RR = 66.67) diarrhea, whereas gefitinib was associated with the lowest risk of all-grade (RR = 2.99) and high-grade (RR = 3.15) diarrhea.

3.4.2. Subgroup analysis according to the tumor types

In order to explore the relationship between EGFR-TKIs associated diarrhea and tumor types, we further analyzed the RRs of diarrhea in patients with NSCLC and non-NSCLC. For all-grade diarrhea, there were significant differences in the RRs by type of cancer ($p = 0.03$, Table 2). All-grade diarrhea were more likely to occur in patients with NSCLC (RR = 4.01) than with non-NSCLC (RR = 2.81). No significant difference was observed in the RRs of high-grade diarrhea by type of tumor ($p = 0.69$, Table 3).

3.4.3. Subgroup analysis according to treatment line

Studies were further stratified according to treatment line (first line, $\geq$second line or maintenance). For both all-grade ($p = 0.39$, Table 2) and high-grade ($p = 0.6$, Table 3) diarrhea, the differences in the RRs by line of therapy was not significant.

3.4.4. Subgroup analysis according to median treatment duration

Studies were further stratified according to median treatment duration (<6 months vs. ≥ 6 months). There was no significant differences in the RRs by type of treatment duration for both all-grade ($p = 0.30$, Table 2) and high-grade diarrhea ($p = 0.05$, Table 3).

3.4.5. Subgroup analysis according to median age

The differences in the RRs by median age (≤ 60 and > 60) were not significant for both all-grade ($p = 0.80$, Table 2) and high-grade diarrhea ($p = 0.09$, Table 3).

3.5. Publication bias

Funnel plots of the studies used in the meta-analysis to evaluate all-grade and high-grade diarrhea are shown in Fig. 4. No significant publication bias was found in the analysis.

4. Discussion

The recent introduction of EGFR-TKIs has opened up a new array of effective and relatively safe drugs for the treatment of patients with NSCLC, thyroid Cancer, breast cancer and other types of cancers. Gastrointestinal AEs in cancer patients remain a significant burden producing morbidity and impacting on optimal dosing for effective treatment. EGFR-TKI-associated diarrhea may become evident as early as 2–3 days after initiation of EGFR-TKI therapy, and may persist for approximately 7 days or longer, often resulting in therapy interruption (Nelson et al., 2013). To the best of our knowledge, this is the first and largest meta-analysis evaluating the risk of diarrhea associated with EGFR-TKIs. Our analysis of data from phase II and phase III RCTs demonstrated a significantly increased risk of all-grade as well as high-grade diarrhea with the use of EGFR-TKIs compared with placebo. The incidence of all-grades and high-grade diarrhea were 3.50 and 8.26 times more likely to occur in patients receiving EGFR-TKIs versus placebo, respectively.

In order to identify potential risk factors, we performed subgroup

Table 1
Characteristics of the included studies.

Study	Phase	Histology	Line of therapy	NO. of patients	Treatment arms	Pts per arm	Median age/ years	Median duration/ months	Median OS/ months	Median PFS/ months	Jadad score	No. of all-grade Diarrhea	No. of high-grade Diarrhea
Arnold et al. (2007)	2	SCLC	First line	105	Vandetanib 300 mg/d	52	56.9	1.75	10.6	2.7	3	42	9
					placebo	53	62.4	3	11.9	2.8		21	1
Lee et al., (2012a)	3	NSCLC	≥second line	922	Vandetanib 300 mg/d	619	60	3.6	8.5	1.9	4	287	34
					placebo	303	60	2.7	7.8	1.8		33	1
Ahn et al. (2013)	2	NSCLC	Maintenance	117	Vandetanib 300 mg/d	75	61	2	15.6	2.7	4	45	2
					placebo	42	60.5	1.9	NR	1.7		4	0
Hsu et al. (2012)	2	HCC	Some	67	Vandetanib 300 mg/d	19	54	1.3	5.75	1.05	4	8	Unclear
					Vandetanib 100 mg/d	25	61	1.4	5.95	1.7		9	Unclear
					Placebo	23	56	1	4.27	0.95		7	Unclear
Wells et al. (2012)	3	Thyroid Cancer	Some	330	vandetanib 300 mg/d	231	50.7	22.5	Unclear	19.3	4	130	25
					placebo	99	53.4	10	Unclear	NR		26	2
Leboulleux et al. (2012)	2	Thyroid Cancer	≥second line	145	Vandetanib 300 mg/d	73	63	Unclear	NR	11.1	5	54	7
					placebo	72	64	Unclear	NR	5.9		12	0
Thatcher et al. (2005)	3	NSCLC	≥second line	1688	Gefitinib 250 mg/d	1126	62	Unclear	5.6	Unclear	5	309	31
					placebo	562	61	Unclear	5.1	Unclear		52	5
Zhang et al. (2012)	3	NSCLC	Maintenance	295	Gefitinib 250 mg/d	147	55	4.9	18.7	4.8	5	37	0
					Placebo	148	55	2.4	16.9	2.6		13	0
Goss et al. (2009)	2	NSCLC	First line	201	Gefitinib 250 mg/d + BSC	100	74	Unclear	3.7	1.4	4	51	3
					placebo + BSC	101	76	Unclear	2.8	1.4		20	3
Dutton et al. (2014)	3	Oesophageal cancer	≥second line	449	Gefitinib 250 mg/d	224	64.7	1.5	3.73	1.57	5	36	13
					placebo	225	64.9	1.2	3.67	1.17		6	2
Gaafar et al. (2011)	3	NSCLC	≥second line	171	Gefitinib 250 mg/d	85	61	3.8	10.9	4.1	3	Unclear	1
					placebo	86	62	2.8	9.4	2.9		Unclear	0
Goss et al., (2013a)	3	NSCLC	Some	492	Gefitinib 250 mg/d	249	66	4.8	61.2	50.4	3	Unclear	25
					placebo	243	67	8.9	NR	38.4		Unclear	7
Cappuzzo et al., (2010)	3	NSCLC	Maintenance	878	Erlotinib 150 mg/d	433	60	Unclear	12	3.1	4	79	7
					placebo	445	60	Unclear	10	2.7		14	0
Kelly et al. (2015)	3	NSCLC	Some	954	Erlotinib 150 mg/d	611	62	11.9	NR	50.5	5	319	38
					placebo	343	61.8	21.9	NR	48.2		54	1
Lee et al. (2012b)	3	NSCLC	First line	647	Erlotinib 150 mg/d	334	77	Unclear	3.7	2.8	5	Unclear	28
					placebo	313	77	Unclear	3.6	2.6		Unclear	4
Shepherd and Rodrigues Pereira (2005)	3	NSCLC	≥second line	727	Erlotinib 150 mg/d	485	62	7.9	6.7	2.2	4	267	29
					Placebo	242	59	Unclear	4.7	1.8		46	2
Miller et al. (2012)	3	NSCLC	≥second line	585	afatinib 50 mg/d + BSC	390	58	10.5	12	3.3	5	339	66
					placebo + BSC	195	59	11	10.8	1.1		18	0
Ellis et al. (2014)	3	NSCLC	≥second line	716	Dacomitinib 45 mg/d	477	63.5	Unclear	6.83	2.66	5	371	59
					Placebo	239	65.5	Unclear	6.3	1.38		36	0
Harrington et al. (2015)	3	SCC	Maintenance	685	Lapatinib 1500 mg/d	349	54	1.6	NR	Unclear	4	148	20
					Placebo	336	55	1.6	NR	Unclear		41	4
Powles et al. (2017)	3	Bladder Cancer	Maintenance	196	Lapatinib 1500 mg/d	97	70.1	5	12.6	4.5	3	65	6
					placebo	99	71.1	Unclear	12	5.1		23	1
Decensi et al. (2011)	2	Breast cancer	First line	60	Lapatinib 1500 mg/d	29	53.6	0.7	Unclear	Unclear	3	18	0
					placebo	31	52.6	Unclear	Unclear	Unclear		5	0
Del Campo et al. (2011)	2	SCC	First line	105	Lapatinib 1500 mg/d	69	58	Unclear	Unclear	Unclear	4	18	Unclear
					placebo	36	55	Unclear	Unclear	Unclear		2	Unclear
Harrington et al. (2013)	2	SCC	Maintenance	66	Lapatinib 1500 mg/d	35	56	13	30.9	35.3	4	15	Unclear
					Placebo	31	57	8	NR	12.1		2	Unclear
Goss et al. (2013b)	3	Breast cancer	≥second line	3147	Lapatinib 1500 mg/d	1573	51	12.5	Unclear	Unclear	5	958	97
					Placebo	1574	52	12.8	Unclear	Unclear		256	9

NSCLC, Non-Small-Cell Lung Cancer; SCLC, Small-Cell Lung Cancer; HCC, Hepatocellular carcinoma; SCC, squamous cell carcinoma; BSC, best support care; NR, not reached.

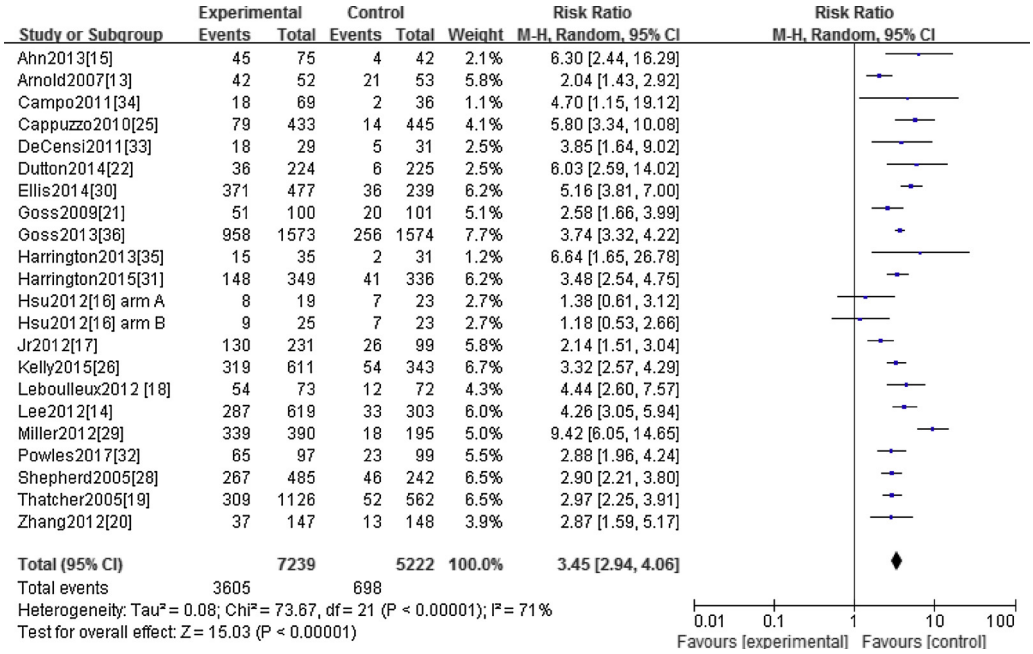

Fig. 2. Forest plots for the risk ratio of All-grade diarrhea.

analysis according to drug types, the risk of all-grade ($p < 0.0001$) and high-grade ($p = 0.02$) diarrhea varied significantly according to drug types. One possible explanation was that different EGFR-TKIs target different receptors, which may lead to different risk of diarrhea. It was noteworthy that afatinib was associated with the highest risk of all-grade and high-grade diarrhea, which was 9.42 and 66.67 times more likely to occur in patients receiving afatinib. One reason for this observation might be a result of afatinib higher affinity for the kinase domain of EGFR than other EGFR-TKIs, and higher potency and broader irreversible ErbB blockade in this setting compared with other EGFR-TKIs (Burstein et al., 2010). Therefore, physician must pay more attention when using afatinib. However, there was only one RCT and 585 patients included in the subgroup analysis of afatinib, more RCTs of adapting afatinib in treating cancer patients should include to confirm this finding in the future research. On the other hand, we found gefitinib was associated with the lowest risk of high-grade and all-grade diarrhea than other EGFR-TKIs, which may provide clinical information to clinicians when using EGFR-TKIs. When stratified by cancer type, the RR of high-grade diarrhea was not affected by cancer type, whereas the RR of all-grade diarrhea varies significantly according to cancer type ($p = 0.03$). This could be due to the fact that different malignancies have different pathogeneses and different spectra of patient comorbidities. Additionally, our subgroup analysis suggested that the RR of all-grade and high-grade diarrhea did not vary significantly according to treatment line, treatment duration, and patient's age.

Diarrhea following treatment with EGFR-TKIs results from the presence of EGFR on cells of epithelial origin, including those of the GI tract. However, the mechanisms underlying diarrhea associated with

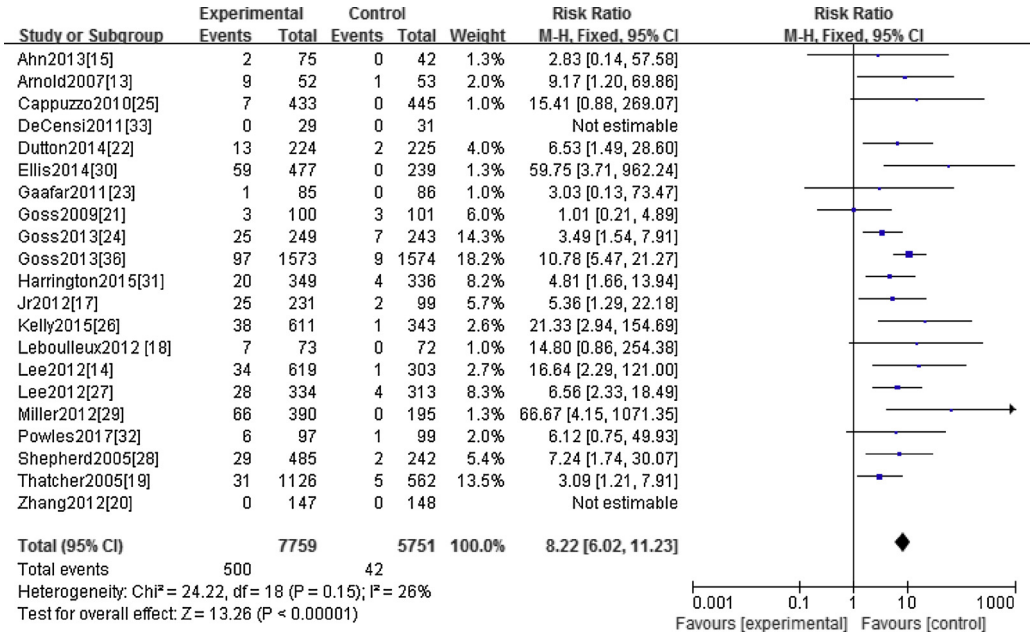

Fig. 3. Forest plots for the risk ratio of high-grade diarrhea.

Table 2
Summary risk ratio (RRs) of all-grade diarrhea associated with EGFR-TKIs in the subgroup analysis.

All-grade Diarrhea	No. of participants	No. of events/Total (%)		RR [95% CI]	p	p-value for group difference
		Treatment	Control			
Type of drug						
Vandetanib	1709	575/1094(52.4)	110/615(17.8)	2.65 [1.77, 3.96]	p < 0.00001	p < 0.0001
Gefitinib	2633	433/1597(27.1)	91/1036(8.8)	2.99 [2.40, 3.73]	p < 0.00001	
Erlotinib	2559	665/1529(43.5)	114/1030(11.1)	3.51 [2.60, 4.74]	p < 0.00001	
Afatinib	585	339/390(86.9)	18/195(9.2)	9.42 [6.05, 14.65]	p < 0.00001	
Dacomitinib	716	371/477(77.8)	36/239(15.1)	5.16 [3.81, 7.00]	p < 0.00001	
Lapatinib	4259	1222/2152(56.8)	329/2107(15.6)	3.66 [3.29, 4.07]	p < 0.00001	
Tumor types						
NSCLC	7083	2104/4463(47.1)	290/2620(11.1)	4.01 [3.15, 5.12]	p < 0.00001	0.03
non-NSCLC	5130	1516/2652(57.2)	422/2478(17.0)	2.81 [2.25, 3.50]	p < 0.00001	
Line of therapy						
First line	366	87/198(43.9)	27/168(16.1)	2.91 [2.00, 4.23]	p < 0.00001	0.39
≥ Second line	8484	2663/5019(53.1)	480/3465(13.9)	3.96 [3.12, 5.02]	p < 0.00001	
Maintenance	2237	389/1136(34.2)	97/1101(8.8)	3.53 [2.80, 4.44]	p < 0.00001	
Median treatment duration						
< 6 months	2919	695/1636(42.4)	160/1283(12.5)	2.98 [2.25, 3.95]	p < 0.00001	0.3
≥ 6 months	5809	2028/3325(61.0)	402/2484(16.2)	3.72 [2.73, 5.07]	p < 0.00001	
Median age						
≤ 60 years	7268	2088/3971(52.6)	445/3297(13.5)	3.35 [2.57, 4.37]	p < 0.00001	0.8
> 60 years	5193	1517/3268(46.4)	253/1925(13.1)	3.49 [2.90, 4.20]	p < 0.00001	

NSCLC, Non-Small-Cell Lung Cancer.

Table 3
Summary risk ratio (RRs) of high-grade diarrhea associated with EGFR-TKIs in the subgroup analysis.

High-grade Diarrhea	No. of participants	No. of events/Total (%)		RR [95% CI]	p	p-value for group difference
		Treatment	Control			
Type of drug						
Vandetanib	1619	77/1050(7.3)	4/569(0.7)	7.88 [3.20, 19.46]	p < 0.00001	0.02
Gefitinib	3296	73/1931(3.8)	17/1365(1.2)	3.15 [1.86, 5.35]	p < 0.0001	
Erlotinib	3206	102/1863(5.4)	7/1343(0.5)	8.44 [4.00, 17.77]	p < 0.00001	
Afatinib	585	66/390(16.9)	0/195(0)	66.67 [4.15, 1071.35]	0.003	
Dacomitinib	716	59/477(12.3)	0/239(0)	59.75 [3.71, 962.24]	0.004	
Lapatinib	4088	123/2048(6.0)	14/2040(0.7)	8.34 [4.80, 14.49]	p < 0.00001	
Tumor types						
NSCLC	6810	301/4057(7.4)	19/2753(0.7)	7.31 [3.58, 14.91]	p < 0.00001	0.69
non-NSCLC	1970	80/1055(7.5)	10/915(1.1)	6.02 [3.17, 11.43]	p < 0.00001	
Line of therapy						
First line	1802	69/1045(6.6)	8/757(1.1)	4.93 [0.98, 24.75]	0.05	0.6
≥ Second line	8655	346/5014(6.9)	20/3551(0.6)	8.55 [4.84, 15.09]	p < 0.00001	
Maintenance	2171	35/1101(3.2)	5/1070(0.5)	5.34 [2.25, 12.64]	p = 0.0001	
Median treatment duration						
< 6 months	3492	110/1926(5.7)	16/1566(1.0)	4.92 [2.94, 8.23]	p < 0.00001	0.05
≥ 6 months	5743	255/3290(7.8)	14/2453(0.6)	10.39 [6.10, 17.67]	p < 0.00001	
Median age						
≤ 60 years	7007	258/3823(6.7)	17/3184(6.7)	11.11 [6.82, 18.09]	p < 0.00001	0.09
> 60 years	6503	242/3936(6.1)	25/2567(1.0)	6.37 [4.24, 9.57]	p < 0.00001	

NSCLC, Non-Small-Cell Lung Cancer.

EGFR-TKI therapy remain poorly understood. One proposed theory is that the diarrhea in this setting is a result of excess chloride secretion, leading to a secretory form of diarrhea. However, it is thought that EGFR-TKI-associated diarrhea is likely to be caused by multiple factors, including: altered gut motility (leading to a shorter transit time through the intestine and reduced water absorption); colonic crypt damage (impairing water absorption in the colon); changes to intestinal microflora (affecting absorption and other intestinal functions dependent on the metabolic activity of the microflora); and altered transport in the colon (Hurvitz et al., 2018).

Diarrhea is defined as three or more watery or loose bowel movements in a 24 h period. The grading system developed by the US National Cancer Institute facilitates the diagnosis and management of this complaint. Early recognition and management of diarrhea is essential to prevent dose reduction or discontinuation of EGFR-TKIs therapy. In the event of grade 1–2 diarrhea, patients should start treatment with loperamide and the EGFR-TKIs treatment should be continued at the same dose. If grade 2 diarrhea persists for more than 48 h, despite antidiarrheal treatment, EGFR-TKIs interruption or dose reduction is recommended. In the event of grade 3 or 4 diarrhea, the patient should be admitted to hospital and aggressive intravenous fluid replacement should be initiated. Patients should continue to receive loperamide treatment, although prophylactic antibiotics can be considered if the patient is neutropenic, and EGFR-TKIs treatment must be interrupted. A recently published study (Hurvitz et al., 2018) demonstrated that loperamide prophylaxis reduces the incidence, severity and duration of EGFR inhibitor induced diarrhea; adding budesonide or colestipol appears to further improve outcomes. Moreover, patient education is essential, and encourages patients to understand the high frequency of diarrhea, the implications of therapy and the purpose of diarrhea management strategies. Additionally, dietary modifications are often beneficial and helpful until the symptoms of diarrhea resolve.

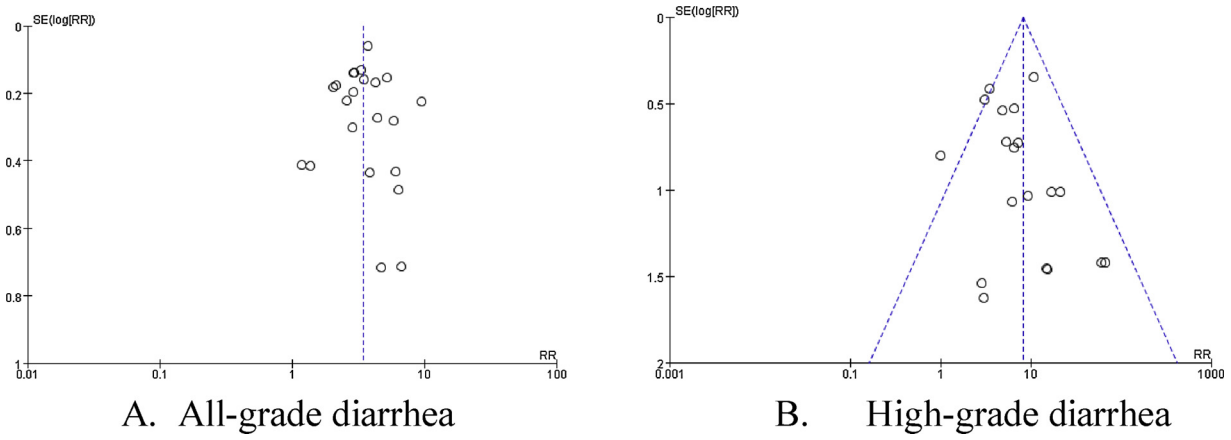

Fig. 4. Funnel plots for all-grade and high-grade diarrhea.

Incorporating bananas, rice, apple sauce and toast, as well as increasing the amounts of clear liquids consumed into the daily diet and avoiding foods/drinks that contain lactose/caffeine, are helpful (Yang et al., 2013).

Despite our efforts to minimize the effects of confounding variables, there were several limitations that need to be considered. First, the data were abstracted from published or presented clinical trial results and were not gathered from individual patient data; thus, the analysis of the factors that potentially contributed to the development of diarrhea, such as prior exposure to gastrointestinal toxic agents or prior radiation therapy, was not possible in this study. Second, the incorporated trials were performed by different researchers from various institutions. Moreover, the diarrhea were defined using different version of CTCAE criteria, which may affect co-primary endpoint. thus, the reported incidence of diarrhea may suffer from potential bias. Also, the varying types of tumors and various EGFR-TKIs examined might enhance heterogeneity. Third, the present meta-analysis mainly included RCTs concerning vandetanib, gefitinib, erlotinib and lapatinib, with only one RCT concerning afatinib and one concerning dacomitinib. Therefore, afatinib- and dacomitinib- induced diarrhea may not be fully reviewed in our research. Ideally, we would include more RCTs of afatinib- and dacomitinib- containing regimens, but we were not aware of any further studies matching these criteria. Furthermore, neratinib is a relatively new TKI associated with high risk of diarrhea, and we should include this agent in our meta-analysis. Several RCTs of neratinib were found in the initial search, but these RCTs could not meet the inclusion criteria. Therefore, we excluded these RCTs from our meta-analysis.

In summary, the current meta-analysis suggests that the use of EGFR-TKIs significantly increase the risk of developing all-grade and high-grade diarrhea in cancer patients. As this class of drugs is used increasingly in patients with various types of cancers, physicians should be aware of this adverse effect and should monitor cancer patients when receiving EGFR-TKIs. Further research is required to enhance our current understanding and develop evidence-based management strategies and risk prediction algorithms for EGFR-TKI-associated diarrhea.

Author contributions

Jing Li was responsible for the conception of the work, wrote the manuscript and study search and selection. Jian Gu contributed to study search and selection and carried out the statistical analyses.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study, formal consent is not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2018.12.001.

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